EXHIBIT H

Asbestos-Related Lung Cancer and Malignant Mesothelioma of the Pleura: Selected Current Issues

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Abstract

Asbestos-related diseases persist, because millions of workers have had prior exposure and many industrializing countries continue to use asbestos. Globally, an estimated 107,000 people die annually from lung cancer, malignant mesothelioma, and asbestosis due to occupational asbestos exposure. Malignant mesothelioma and lung cancer are caused by all major types of asbestos. Asbestos causes more lung cancer deaths than malignant mesothelioma of the pleura; most cases of the latter are due to asbestos exposure. The cancer risk increases with cumulative asbestos exposure, with increased risk even at low levels of exposure to asbestos. Based on empirical studies, an estimated cumulative occupational exposure to asbestos of 1 fiber/mL-year substantially raises malignant mesothelioma risk. No safe threshold for asbestos exposure has been established for lung cancer and mesothelioma. The validity of fiber-type risk assessments depends critically on the quality of exposure assessments, which vary considerably, leading to a high degree of uncertainty. Asbestos exposure without asbestosis and smoking increases the risk of lung cancer. The joint effect of asbestos and smoking is supra-additive, which may depend in part on the presence of asbestosis. Asbestos workers who cease smoking experience a dramatic drop in lung cancer risk, which approaches that of nonsmokers after 30 years. Studies to date show that longer, thinner fibers have a stronger association with lung cancer than shorter, less thin fibers, but the latter nonetheless also show an association with lung cancer and mesothelioma. Low-dose chest computed tomographic scanning offers an unprecedented opportunity to detect early-stage lung cancers in asbestos-exposed workers.

Keywords

- asbestos
- lung cancer
- malignant mesothelioma
- asbestosis
- chrysotile

Asbestos, the cause of the most important occupational disease epidemic of the 20th century into the 21st century, remains highly relevant to public health even as it has largely disappeared from manufacture and new uses in the United States, Europe, Japan, and Australia. First, despite its ban from use and manufacture in 55 countries, asbestos continues to be mined and formulated into new products in many countries, most notably in China, India, Russia, and Brazil. Indeed, in 2011, China used nearly as much asbestos, 638,000 metric tons, as the United States used in its peak year of consumption, 1973.[1] World Health Organization (WHO) estimates that there are currently approximately 125 million people in the world who are exposed to asbestos in the workplace.[2] Second, most asbestos that was ever used in industrialized countries still remains in place and thereby presents and will continue to offer opportunities for exposure for workers in renovation, maintenance, demolition, and waste removal. Third, there is a large reservoir of people in industrialized countries who,

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despite cessation of exposure, had significant exposure to asbestos in the past. In the United States, for example, there are an estimated 10 to 15 million people who have had prior exposure to asbestos, and, therefore, remain at risk for asbestos-related diseases.

Incidence and Prevalence of Asbestos-Related Diseases of the Chest

According to the most recent WHO estimates, more than 107,000 people die each year on a global basis from asbestos-related lung cancer, malignant mesothelioma, and asbestosis resulting from exposure at work.[2] Approximately one-half of all deaths due to occupational cancer are estimated to be caused by asbestos. In addition, it is estimated that several thousand deaths annually can be attributed to exposure to asbestos in the home.[2,3]

The most accurate data on the burden of asbestos-related diseases are the estimated counts of cases of malignant mesothelioma due to its highly specific association with prior exposure to asbestos. There are an estimated 28,000 to 43,000 deaths from malignant mesothelioma worldwide per year.[4,5] In addition, based on asbestos consumption patterns, it is believed that there are many more unrecognized malignant mesothelioma deaths in countries with no or little reporting, including Russia, China, India, and Kazakhstan.[5] The highest malignant mesothelioma incidence in the world occurs in the United Kingdom and Australia and is approximately 30 cases per million people per year compared with 8 and 10 cases per million people per year in the United States and Japan, respectively.[6] In the United Kingdom, malignant mesothelioma caused 1,749 deaths in men in 2005, constituting 1 in 40 cancer deaths among men younger than 80 years.[7] The incidence of malignant mesothelioma is not expected to peak in many industrialized countries until the next one to two decades due to historical patterns of asbestos consumption.

Lung cancer caused by asbestos is generally more frequent than malignant mesothelioma, even if cases of the latter disease are far more likely to be recognized as being caused by asbestos. The under-recognition of lung cancer caused by asbestos is widely reported.[8] The ratio between the numbers or incidence of these two diseases varies considerably in individual studies,[8] though a commonly used ratio of excess asbestos-related lung cancers to malignant mesothelioma is 2:1.[8,9] Because occupational asbestos exposure was reasonably common in industrialized countries between the 1940s and the 1980s, asbestos-related lung cancer constitutes a significant proportion of all lung cancers occurring in those countries. Accumulated studies indicate that approximately 4 to 10% of lung cancer in most developed countries is due, at present or in the recent past, to asbestos exposure.[9–12] McCormack and colleagues applied two models to estimate asbestos-related lung cancer mortality based on mesothelioma mortality in 20 countries and obtained a broad range of proportions of lung cancer that are ascribed to asbestos, ranging from 3.2 to 5.4% in the United States to 12.2 to 16.2% in the United Kingdom.[9]

Malignant Mesothelioma

Diffuse malignant mesothelioma, a primary cancer of mesothelial serosa, occurs in four anatomic locations: the pleura, the peritoneum, the pericardium, and the tunica vaginalis (the serous covering of the testis). Approximately 90% of malignant mesotheliomas occur in the pleura, and most of the remaining cases occur in the peritoneum.[13–15] Regardless of location, asbestos is the common etiology for the majority of malignant mesotheliomas.

Malignant mesothelioma is caused by all types of asbestos, including chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite.[16] This conclusion is based on epidemiological, experimental, and mechanistic studies and reflects a broad consensus of views in the scientific, public health, and regulatory communities.[3,16–22]

Asbestos is the dominant cause of human malignant mesothelioma and is responsible for at least 85 to 90% of pleural malignant mesothelioma among men. Indeed, over time, as the methods of identifying historical asbestos exposure have improved, the proportion of cases of malignant mesothelioma that were preceded by an identified exposure to asbestos has increased. Leigh and Driscoll reported from the Australian Mesothelioma Registry that 90% of male cases and 61% of female cases reported a history of asbestos exposure.[13] As importantly, of cases without an identified history of asbestos exposure, most (81%) had lung fiber counts $>$ 200,000 asbestos fibers/g dry lung, indicating prior exposure to asbestos. Thus, the vast majority of the malignant mesothelioma cases in their registry had a prior history of exposure to asbestos. In a national Italian study using detailed mesothelioma registry data, Marinaccio et al found that 87 and 80% of male cases of pleural and peritoneal mesotheliomas, respectively, reported a history of asbestos exposure, usually occupational in origin.[14] Comparable data for women in Italy showed that 63 and 53% of cases of pleural and peritoneal mesotheliomas, respectively, reported a history of asbestos exposure, though in many instances it was nonoccupational in origin.[14] In a national population case–control study of pleural malignant mesothelioma in France, Lacourt et al found that 95 and 75% of male and female cases of pleural malignant mesothelioma, respectively, reported asbestos exposure or were judged to have been exposed to asbestos.[23] From the same study, the population-attributable risk of pleural malignant mesothelioma due to asbestos exposure was 87% among men and 65% among women.[23] Rake and British colleagues conducted a large mesothelioma case–control study in the United Kingdom, based on direct interviews with study participants, and found that 85% of male cases and 38% of female cases were associated with a prior exposure to asbestos.[24] They noted that many additional female cases of malignant mesothelioma may be associated with exposure to asbestos in settings that the authors had considered to be low risk.[24] In Mexico, Aguilar-Madrid et al studied 177 cases of pleural malignant mesothelioma and found that 81% had had occupational exposure to asbestos.[25]

Other established causes of malignant mesothelioma are the mineral fibers, erionite and fluoro-edenite, that have

caused malignant mesothelioma in specific geographic regions in Turkey and Sicily, respectively.[26,27] Radiation for Hodgkin lymphoma and non-Hodgkin lymphoma has been associated with an increased risk of malignant mesothelioma.[28–30] The DNA virus, SV40, has been studied in relation to mesothelioma induction with conflicting results. A recent review by the International Agency for Research on Cancer determined that there is inadequate evidence to consider SV40 a human carcinogen.[31]

Exposure–Response: Asbestos Exposure and Malignant Mesothelioma

The risk of malignant mesothelioma due to asbestos is dose dependent, as amply demonstrated in many occupational cohort studies across a range of industries. Malignant mesothelioma is known to occur at lower levels of exposure to asbestos, and no dose has been established below which there is no risk of malignant mesothelioma; that is, no "safe" threshold of cancer risk has been demonstrated.

►**Table 1** summarizes findings from several large case–control studies of malignant mesothelioma undertaken in numerous countries that evaluated the risk of mesothelioma by estimated occupational asbestos exposure. Case–control studies of malignant mesothelioma have selected advantages, because they concentrate large numbers of cases of malignant mesothelioma, which usually occur in relatively small numbers (i.e., < 20 cases) in individual studies of asbestos-exposed cohorts. They also usually capture a set of cases of malignant mesothelioma with diverse histories of asbestos exposure, permitting evaluation of risk associated with differing levels of exposure. All studies in ►**Table 1** show a sharp rise in mesothelioma risk with increasing asbestos exposure. This pattern signifies that at any level of occupational asbestos exposure, adding additional occupational exposure to asbestos increases the likelihood of developing malignant mesothelioma.

There are three consequences of this observed exposure–response pattern. First, for the individual who has had some occupational asbestos exposure, it is essential to avoid additional exposure to asbestos, because it adds, often dramatically, to their risk of developing malignant mesothelioma. Second, in terms of attribution of malignant mesothelioma to prior asbestos exposure, it is clear that each increment in occupational asbestos exposure contributes significantly to

Table 1 Risk of malignant mesothelioma according to levels of occupational asbestos exposure: results of case–control studies

Cumulative exposure (fiber/mL-year)	Cases/controls	Odds ratio	95% CI
French study[32] no. 1			
Not exposed	95/154	1.0	–
0.001–0.49	77/109	1.2	0.8–1.8
0.5–0.99	29/12	4.2	2.0–8.8
1–9.9	80/27	5.2	3.1–8.8
≥ 10	49/10	8.7	4.1–18.5
German study[33]			
Not exposed	11/67	1.0	–
> 0–0.15	14/12	7.9	2.1–30.0
> 0.15–1.5	38/25	21.9	5.7–83.8
> 1.5–15	46/16	47.1	11.5–193
> 15	16/5	45.4	8.1–257
French study[23] no. 2 (males only)			99% CI
Not exposed	28/327	1.0	–
> 0–0.1	54/181	4.0	1.9–8.3
> 0.1–1	68/121	8.3	3.8–17.7
> 1–10	115/68	22.5	10.4–48.7
> 10	97/27	67.0	25.6–175.1
Intensity of exposure	Cases/Controls	Odds ratio	95% CI
Spanish study[42]			
Not exposed	30/127	1.0	–
Low	35/70	3.35	1.72–6.52
Medium	25/18	9.96	4.38–22.7
High	22/6	27.1	9.28–79.3

Abbreviation: CI, confidence interval.

the development of mesothelioma in the group. For example, as shown in ►Table 1, in the two French and the German case–control studies, adding up to 1 fiber/mL-year of exposure to the lowest category of asbestos exposure elevates the exposed persons to the next higher category of asbestos exposure and doubles or triples the risk of malignant mesothelioma.[23,32,33] Third, finding excess cancer risk at low levels of occupational exposure to asbestos supports the notion that there is no safe level of exposure to asbestos.

Low Level of Asbestos Exposure and Mesothelioma

It has long been known that relatively low doses of asbestos can cause malignant mesothelioma. Malignant mesotheliomas have been documented among neighborhood residents of asbestos-using factories[34–36]; community residents of asbestos mining areas[37,38] and household residents of asbestos workers, including peritoneal mesothelioma.[34,39,40] Given the rarity of malignant mesothelioma in the population in the absence of asbestos exposure, these documented exposure-disease links demonstrated that asbestos exposure outside of the occupational environment causes malignant mesothelioma.

Magnani et al examined nonoccupational asbestos exposure in a case–control study of pleural mesothelioma in Italy, Spain, and Switzerland.[41] They found an odds ratio (OR) of 4.8 (95% confidence interval [CI]: 1.8–13.1) for domestic exposure to asbestos and an OR of 11.5 (95% CI: 3.5–38.2) for neighborhood exposure to asbestos, that is, living within 2,000 m from an asbestos-using facility.[41] There also was a clear dose–response relationship between environmental and domestic exposure to asbestos and mesothelioma.

Recent studies have provided a more quantitative evaluation of the risk of malignant mesothelioma at lower levels of exposures in occupational settings (►Table 1).[23,32,33,42,43] These studies employed job histories and industrial hygiene expert assessments of the level, timing, and likelihood of asbestos exposures by occupation and industry. Iwatsubo and colleagues queried 405 cases of malignant mesothelioma in a French case–control study between 1987 and 1993 and found that cumulative asbestos exposure of 0.5 to 0.99 fiber/mL-year, even if the exposure was intermittent, was associated with an OR of 4.2 (95% CI: 2.0–8.8). Higher doses led to higher risks.[32] Rödelsperger et al performed a case–control study in Germany with 125 male cases of malignant mesothelioma and found an OR of 7.9 (95% CI: 2.1–30.0) and 21.9 (95% CI: 5.7–83.8) among the groups with up to 0.15 fiber/mL-year and between $>$0.15 and 1.5 fiber/mL-year, respectively.[33] In a second French national population case–control study of pleural malignant mesothelioma, Lacourt et al found that cumulative exposure to asbestos among men below 0.1 fiber/mL-year was associated with an OR of 4.0 (99% CI: 1.9–8.3), which doubled to an OR of 8.3 (99% CI: 3.8–17.7) for cumulative exposure $>$0.1 to 1.0 fiber/mL-year.[23] They also found a clear dose–response relationship between exposure to asbestos and malignant mesothelioma. Offermans et al (not shown in ►Table 1), using an established Finnish job-exposure matrix in a large Netherland cohort study, found a relative risk (hazards ratio) of 2.7 (95% CI: 1.6–4.5) for the group with the lowest level of asbestos exposure (median cumulative exposure = 0.2 fiber/mL-year).[43] Agudo et al studied 132 cases of pleural mesothelioma in Spain in a case–control study and found that “low-intensity” occupational exposure was associated with an OR of 3.4 (95% CI: 1.7–6.5).[42]

To place these levels of asbestos exposure in perspective, the current legal 8-hour permissible exposure level to asbestos in the United States and the United Kingdom is 0.1 fiber/mL air.[18,44,45] A 45-year working career at this level yields a cumulative exposure to asbestos of 4.5 fiber/mL-year. Both Occupational Safety and Health Administration (OSHA) and the Health and Safety Executive of the United Kingdom assert that the regulated level is not safe. Indeed, OSHA estimates that 2 to 3 excess chest cancers per 1,000 workers exposed at 0.1 fiber/mL for 45 years will occur.[45] Both agencies mandate work practices and engineering controls that effectively lower the exposure to asbestos for workers.

Chrysotile as a Cause of Malignant Mesothelioma

There is a broad consensus that chrysotile asbestos causes human malignant mesothelioma.[16–18,46–48] This causal relation is important not only for the scientific understanding of fiber toxicology but also for its relevance to prevention, public health, public policy, and compensation for people who have developed malignant mesothelioma. First, banning all use of asbestos, including chrysotile, has been adopted by 55 countries and is widely supported.[47,49] However, chrysotile asbestos remains in use and is the only type of asbestos that is still mined and formulated into new products, almost exclusively in industrializing countries. Until a global ban is achieved, countries, enterprises, and workers who continue to use chrysotile asbestos must have an unqualified understanding that they use a known human carcinogen and must be protected from exposure. Second, 95% of asbestos that has been used in the United States, and much of the asbestos that was used in other countries, has been chrysotile asbestos, and much of this asbestos remains in buildings and equipment, thereby posing a current and future hazard to a broad range of occupations that repair, maintain, renovate, and demolish those buildings and equipment. Third, to the extent that compensation proceedings attempt to attribute mesothelioma risk to different products or asbestos fiber types, the recognition that chrysotile asbestos causes malignant mesothelioma is an essential element in decision making.

The scientific basis for the mesothelial carcinogenicity of chrysotile is an established body of published epidemiological studies, animal carcinogen assays, and pleural fiber burden studies. These have been reviewed elsewhere.[16,17,19,21,47,50]

Epidemiological studies have shown that malignant mesothelioma has developed among a variety of workers whose exclusive or near-exclusive exposure to asbestos was to chrysotile asbestos. Examples include the Quebec chrysotile miners and millers (33 cases of malignant mesothelioma)[51]; workers who were active at the chrysotile mines in Balangero, Italy, or used the mine products (17 cases of malignant mesothelioma)[38]; textile workers at North Carolina textile plants (8 cases of mesothelioma and pleural cancer)[52]; textile workers at a South Carolina plant (3 malignant

mesothelioma)[53]; railroad machinists (14 malignant mesotheliomas)[54]; and workers in a friction products plant (6 cases of malignant mesothelioma).[55,56] In addition, malignant mesothelioma has been associated in neighborhood or household settings with levels of exposure to chrysotile that are generally less than those seen in companion occupational environments, including seven cases of malignant mesothelioma among Quebec residents in mining areas[37] and five cases following household or environmental exposure to chrysotile in relation to the Balangero mine.[38]

The availability of airborne asbestos measurements and mesothelioma mortality data in a limited number of asbestos cohorts has permitted the estimation of mesothelioma risk per unit dose, usually measured in fiber/mL-year. Aggregation of these studies[19,20] and meta-analyses[57] have been performed to identify sources and levels of variation in risk by industry type and by fiber type. Per unit dose, crocidolite exposure is associated with a higher risk of mesothelioma than chrysotile. Amosite also appears to be associated with a somewhat higher risk of mesothelioma than chrysotile though less so than crocidolite. Nicholson estimates that crocidolite is 4 to 10 times more potent than chrysotile and that chrysotile and amosite are roughly equipotent.[20] In an analysis published in 2000, Hodgson and Darnton[57] used a different measure of risk and found a potency ratio for crocidolite:amosite:chrysotile of 500:100:1. However, recent studies[52,58] have raised doubts and led to revisions in the estimates developed by Hodgson and Darnton. A new study of mortality at three North Carolina textile plants[52] caused Hodgson and Darnton to revise their fiber potency ratios for malignant mesothelioma downwards sevenfold to 70:14:1 for crocidolite:amosite:chrysotile.[58] Additional studies[38,56] have updated the mortality experience of two of the chrysotile asbestos cohorts originally studied by Hodgson and Darnton but have not yet been addressed in a revised meta-analysis. Both of these studies have described additional mesothelioma deaths in their respective cohorts. These include (1) an update of the chrysotile miner cohort in Balangero, Italy, where 14 workers active in mine operations and an additional 13 other exposed individuals have developed malignant mesothelioma,[38] and (2) an update of mesothelioma cases in the Connecticut friction product plant, where additional cases of malignant mesothelioma have been documented.[56]

Two outstanding considerations—one scientific and the other practical—color the reliability and significance of putative differences in fiber-specific potency in causing malignant mesothelioma. First, the difficulties in ascertaining mesothelioma deaths over the relevant decades and the highly variable quality in exposure assessments in different study settings temper the validity of study results to form the basis of risk estimates. Many of the relevant individual study exposure assessments have been found to be lacking for numerous reasons: (1) restriction of fibers counted by phase contrast microscopy to fibers $\geq$ 5 μm in length and >0.25 μm in width, thereby failing to count the majority of chrysotile fibers; (2) variation in counts by different phase contrast microscopes; (3) variation in counting methods between laboratories and over time; (4) use of area samples to characterize personal exposures; (5) absence of, or a limited number of, measurements from selected periods in the history of the study site; (6) incomplete work histories; and (7) uncertain and variable conversion of fiber counts from one method (e.g., midget impinger-based dust particle counts in millions of particles per cubic foot) to another (fiber counts by phase contrast microscopy).[8,59,60] Such limitations formed an important basis for the U.S. Environmental Protection Agency (EPA) to reject a proposed update of asbestos risk assessment in 2008.[61] The International Agency for Research on Cancer recently reviewed this issue and concluded that "there is a high degree of uncertainty concerning the accuracy of the relative potency estimates … because of the severe potential for exposure misclassification in these studies" (p. 239).[16]

The other relevant consideration to the relative importance of fiber type for public health is the quantity of different fiber types used. In the United States, 95% of asbestos used in the 20th century was chrysotile, so that for the majority of workers who worked with or near asbestos, chrysotile was, and still remains, the dominant fiber type to which they were exposed. At present, chrysotile is the exclusive or near exclusive fiber mined and used in new products throughout the world, so its potency in causing mesothelioma relative to other asbestos fiber types becomes less relevant.

Rat inhalation and intrapleural injection studies have compared mesothelioma tumor production in response to exposure to the different types of asbestos.[16] Rat inhalation studies show relatively low percentages of animals developing mesotheliomas, but the highest percentage of mesotheliomas was found in animals exposed to chrysotile. Wagner found 2.9% of chrysotile-exposed animals developed mesotheliomas versus 0.7 to 2.8% among the animals exposed to various amphiboles.[62] Davis et al also found mesotheliomas among rats exposed to chrysotile in inhalation studies, though fiber length confounded the findings.[63] Intrapleural and intraperitoneal injection studies in different strains of rats show high proportions of tested animals developing mesotheliomas in response to various types of asbestos, including chrysotile.[16]

Fiber burden studies characterize the concentrations of fibers in tissues. Because they are performed on tissues obtained at the time of biopsy, surgery, or autopsy, they characterize fiber concentrations after the tumor has been clinically detected. This presents a challenge for causal inference, as the critical events that caused neoplastic transformation are believed to have occurred many years previously, when the profile of fiber concentration in relevant tissues may have been quite different. Additional constraints of this approach include (1) the absence of a widely used and accepted standard method for conducting tissue fiber counts; (2) the restriction of fiber burden studies to a limited number of individuals who may not be representative of defined asbestos-exposed populations; (3) the use of different microscopes (phase contrast microscopy, scanning electron microscopy, and transmission electron microscopy [TEM]) at varying magnifications that can detect and count different populations of fibers; (4) ranges of "normal" fiber counts in

populations without known occupational exposure to asbestos that vary from one laboratory to the next; and (5) the difficulty of inferring from an organ or tissue where a fiber burden study is performed to the organ or tissue where the disease occurs.[64–66] This last issue applies to the relevance of lung fiber burden counts to the occurrence of malignant mesothelioma.

Multiple studies have found a dominance of chrysotile fibers, and sometimes exclusively chrysotile fibers, in pleural tissue and in pleural mesothelioma tissue.[67–69] Sebastien et al reported finding mostly short chrysotile fibers (84% $\leq$ 4 µm in length) in parietal pleura from a mixture of cases with nonmalignant and malignant asbestos-related diseases.[67] Suzuki and Yuen[69] used TEM to measure lung fiber burden in lung, plaque, and mesothelioma tissue in 168 cases of malignant mesothelioma and found that chrysotile was the sole asbestos type found in the mesothelioma tumor tissue in 73% (90/123) of mesothelioma cases and in the lung in 26% (31/119) of mesothelioma cases. Only 1% of chrysotile fibers were $\geq$ 5 µm in length.[69]

Lung Cancer

Asbestos is universally recognized as a human lung carcinogen.[2,16,17] Like malignant mesothelioma, all of the major asbestos fiber types—chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite—are established as causing lung cancer, based on the cumulative scientific evidence provided by animal experiments, epidemiologic and pathology studies, and mechanism-based research.[16,17]

The International Agency for Research on Cancer and others have recently reviewed over 60 epidemiologic studies that examined the relation between occupational exposure to asbestos and lung cancer.[9,16,70] Most studies showed excess risk of lung cancer from asbestos exposure. The considerable differences in the level of excess risk of lung cancer among different epidemiological studies vary according to a large number factors, including study methods, data quality, reference populations, age structure of study population, country, occupation, industry, industrial process, job tasks, calendar years, exposure intensity and duration, fiber type, fiber dimensions, smoking information, the presence of other lung carcinogens, and others. The best studied contrast in lung cancer risk in different exposure settings is between the Quebec mines and mills,[71] where excess lung cancer risk is modest, and the textile factory in South Carolina,[53] where the risk of lung cancer is much higher. Notably, in both settings, Canadian chrysotile asbestos was used.

Dose–Response: Asbestos Exposure and Lung Cancer

Lung cancer risk increases with cumulative exposure to asbestos.[8,48,60,70,72] Studies of sufficient size and with quantitative exposure assessments have permitted estimation of lung cancer risk at different levels of exposure to asbestos. The slope of the resultant line that characterizes the relationship between exposure and lung cancer represents the potency of asbestos to cause lung cancer for a particular study (K_L in the published literature). These studies have principally been of cohorts in asbestos textile, cement and friction products manufacturing, insulation, and mining and milling. In general, the increase in lung cancer relative risk has been found to be from 1 to 4% for each year of exposure to 1 fiber/mL (i.e., fiber/mL-year).[70] The exposure–response relationship is considered to be approximately linear.[8,70] Indeed, available meta-analyses generally assume a linear dose–response relationship between asbestos exposure and lung cancer.[57,60,70,72] Most individual studies to date have involved relatively heavy exposure to asbestos, and the lung cancer risk at lower levels is then extrapolated from these studies, or is based on the relatively few studies of lower level exposure to asbestos.[72] A recent meta-analysis that was based on a nonlinear metaregression model (i.e., a natural spline model) used all available published data on exposure–response relationships at lower levels of asbestos exposure, thereby obviating the need to depend solely on extrapolating from high level exposure results.[72] The results demonstrated a higher level of lung cancer risk increment per fiber/mL-year for relatively low levels of asbestos exposure compared with previous meta-analyses.[72]

As noted in the previous section on malignant mesothelioma, a critical source of variation and error in evaluating exposure–response relationships in asbestos is the validity of exposure estimates of the relevant studies. These limitations introduce measurement error, which often leads to the underestimation of relative risk. Importantly, Lenters et al found higher estimates of lung cancer risk due to asbestos in studies that had higher quality exposure assessments, which is likely to explain some of the variability in results among studies.[60]

Role of Asbestosis in Lung Cancer Risk

The relationship between asbestos exposure, asbestosis, and lung cancer risk has long been studied and is complicated, mainly because the risk and intensity of asbestosis increases with increasing asbestos exposure and because study information on the three key lung cancer risk factors—asbestos exposure, asbestosis, and smoking—is incomplete or imprecise in many studies. Nonetheless, it is clear that asbestos exposure in the absence of evidence of asbestosis raises the risk of lung cancer, and the added presence of asbestosis further raises the lung cancer risk.

Asbestos exposure in the absence of asbestosis increases the risk of lung cancer among a variety of different asbestos workers, as supported by a substantial published literature.[73–81] The range of elevation in lung cancer risk in these studies is approximately 1.5 to 5.5. In a recent update of the mortality of a large North American insulator cohort, Markowitz et al compared long-term insulators to a blue collar control group without asbestos exposure that was part of the Cancer Prevention Study II of the American Cancer Society.[81] They found a lung cancer mortality rate ratio of 3.6 (95% CI: 1.7–7.6) among long-term insulators who had never smoked and had no radiographic evidence of asbestosis compared with the blue collar controls.[81]

Asbestosis, usually documented by chest imaging studies, increases the risk of lung cancer, as seen in cohort studies of

asbestos cement workers,[74] asbestos textile workers,[76] and asbestos miners.[77,82] The range of elevations in the standardized mortality ratios for lung cancer was 194 to 996; these elevations were statistically significant. Control for cigarette smoking was rare in these studies, but the magnitude of elevation in lung cancer risk is highly unlikely to have been caused by cigarette smoking alone.[83] In the study noted earlier, Markowitz et al found a doubling of risk of lung cancer among long-term insulators with asbestosis compared with insulators without asbestosis, both among never smokers and smokers. The duration and extent of asbestos exposure was similar among the insulators with and without asbestosis; therefore, the difference in lung cancer risk between the two groups was not likely to be due to differences in asbestos exposure.[81]

Lung Cancer among Asbestos-Exposed Nonsmokers

Asbestos exposure alone, in the absence of cigarette smoking, causes lung cancer. Hammond et al identified a fivefold increase in lung cancer mortality rate ratio among nonsmoking long-term insulators in their study of 17,800 insulators.[84] Soon thereafter, McDonald and colleagues reported a dose-related increase in lung cancer deaths among nonsmoker Quebec miners and millers.[85] Berry et al identified mortality among 1,670 asbestos factory workers between 1971 and 1980 and found a relative risk of lung cancer of 7.3, based on 4 lung cancers, among never smokers.[86] Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls from 1972 to 2008 and found an overall age-adjusted lung cancer hazard ratio of 7.5 (95% CI: 0.9–62.8) among nonsmoker workers.[87] In one of the largest relevant studies, Markowitz followed 2,377 insulators from 1981 to 2008 and found a lung cancer mortality rate ratio of 5.2 (95% CI: 3.2–8.5) among nonsmokers, based on 18 lung cancer deaths among nonsmokers.[81]

Joint Effect of Asbestos Exposure and Cigarette Smoking in Lung Cancer

The joint effect of asbestos and cigarette smoking in causing lung cancer is widely cited in epidemiology and public health as a classic example of interaction between causes. The best known study of this topic is that published by Hammond et al, who found a multiplicative effect between the asbestos exposure and smoking in elevating lung cancer mortality among 17,800 insulators whose deaths occurred in 1967 to 1976, compared with a blue collar cohort from the Cancer Prevention Study I of the American Cancer Society followed over the same time period. Insulators who had never smoked had a lung cancer death rate ratio of 5.2, compared with the never-smoking control group. The lung cancer mortality ratio in the smoking control group without asbestos exposure was 10.9, and the lung cancer mortality ratio among smoking insulators was 53. The joint effect of asbestos and smoking was multiplicative.[84]

At least two dozen published studies have addressed the issue of the relation between smoking and asbestos exposure in elevating lung cancer risk.[88–90] Viewed in aggregate, the existing literature favors a joint effect of asbestos and smoking that is synergistic, and, more specifically, greater than additive but probably less than multiplicative.[70,88,90] Some studies, however, have found a joint multiplicative effect. Central to the difficulty in studying this issue is the dearth of lung cancers among never smokers, including among asbestos-exposed workers, especially among smaller studies.

Recent studies tend to confirm that the joint effect of asbestos and smoking is more than additive but less than multiplicative. Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls in China from 1972 to 2008. Among nonsmoking workers exposed to asbestos, the hazard ratio for lung cancer was 7.5 (95% CI: 0.9–62.8).[87] Smokers from a non–asbestos-exposed control group had a lung cancer hazard ratio of 6.0. The asbestos workers who smoked had a lung cancer hazard ratio of 17.4, indicating a supra-additive effect of asbestos and smoking, though the effect did not reach statistical significance.[87] Offermans and colleagues studied >120,000 people in the Netherlands Cohort Study and found a lung cancer hazard ratio of 1.79 (95% CI: 1.04–3.08) among never smokers who had a history of asbestos exposure. The corresponding hazard ratio among current smokers never exposed to asbestos was 7.48 (95% CI: 5.55–10.08). The joint hazard ratio was 10.21 (95% CI: 7.26–14.35), suggesting a joint effect that was midway between additive and multiplicative.[43] Reid et al also found a supra-additive effect among Wittenoom miners and millers in Australia.[91]

The source of some of the variation in the empirical studies of the joint effect of asbestos and smoking in causing lung cancer has recently been clarified. Markowitz et al described mortality patterns from 1981 through 2008 for 2,377 North American insulators for whom information on smoking, asbestos exposure, and radiographic findings of asbestosis were available.[81] The study had a relatively high number of lung cancer deaths among asbestos-exposed workers who had never smoked ($n = 18$). They found that the lung cancer rate ratio was 3.6 (95% CI: 1.7–7.6) for nonsmoking insulators without asbestosis; 10.3 (95% CI: 8.8–12.2) among the smoking control group; and 14.4 (95% CI: 10.7–19.4) among insulators who had smoked but had no asbestosis. Among nonsmoking insulators with asbestosis, the lung cancer mortality rate ratio was 7.4 (95% CI: 4.0–13.7); 10.3 (95% CI: 8.8–12.2) among the smoking control group; and 36.8 (95% CI: 30.1–45.0) among insulators who had smoked but also had asbestosis.[81]

Smoking Cessation and Lung Cancer Risk

The issue of what happens to lung cancer risk when asbestos-exposed workers stop smoking is not only of obvious public health importance but also of scientific interest, given the facts that lung cancer risk increases with time following asbestos exposure but decreases with time following smoking cessation. Reid et al followed 2,935 Australian miners and millers from 1979 to 2002 and found that lung cancer risk generally diminished following smoking cessation but may remain elevated with an OR of 1.9 (95% CI: 0.50–7.2) in subjects $\geq$ 20 years since quitting smoking.[91] Frost et al examined lung cancer mortality among 98,912 asbestos

workers in Great Britain between 1971 and 2005 and found that lung cancer mortality reduced following smoking cessation but remained possibly elevated ≥ 40 years following smoking cessation (relative risk = 1.5, 95% CI: 0.8–2.8).[92] Markowitz and colleagues traced mortality among 2,377 insulators from 1981 to 2008, including the nearly 60% of smoking insulators who had quit smoking. They found that lung cancer rate ratios dropped by one-half during the first 10 years following smoking cessation and continued to decrease thereafter. Former smoking insulators with ≥ 30 years following cessation had the same lung cancer risk as insulators who had never smoked cigarettes.[81]

Fiber Type and Lung Cancer Risk

Chrysotile asbestos causes lung cancer, as supported by a large body of published epidemiological studies, animal carcinogen assays, and mechanistic studies. These studies have been reviewed.[16,17,19,21,50,70]

Recent examples of excess lung cancer mortality among workers exposed to chrysotile asbestos are multiple. Wang et al followed 577 chrysotile asbestos manufacturing workers and 435 blue collar controls from 1972 to 2008 in China and found an age- and smoking-adjusted overall hazard ratio of 3.31 (95% CI: 1.60–6.87) for lung cancer among asbestos-exposed workers.[87] Loomis and colleagues identified mortality patterns among workers at four North Carolina textile plants that used almost exclusively chrysotile asbestos and found a standardized mortality ratio (SMR) of 1.96 (95% CI: 1.73–2.20); 277 workers had died from cancer of the lung or trachea.[52] Hein et al updated the mortality of the South Carolina textile factory cohort where > 99.9% of the asbestos used was chrysotile and found a lung cancer standardized mortality ratio of 1.95 (95% CI: 1.68–2.24).[53]

As in the case of malignant mesothelioma, the relative potency of different types of asbestos in causing lung cancer has been evaluated. Some meta-analyses of asbestos exposure and lung cancer studies have shown an increased potency for amphiboles relative to chrysotile in causing lung cancer by approximately 5- to 10-fold.[57,93] A more recent meta-analysis that used a different meta-regression modeling method found a nonsignificant three- to fourfold difference in potencies between chrysotile and amphiboles.[72] A recent meta-analysis that factored in quality of exposure assessments of included studies concluded that potency differences among fiber types narrowed after taking into account quality of exposure assessment and that potency differences were inconclusive when analysis was restricted to studies with higher quality exposure assessments.[60]

In a recent systematic review, Nielsen et al (2014) evaluated existing studies and concluded that "all types of asbestos fibers are associated with lung cancer …. (and) there is not sufficient evidence to derive different risk estimates for different fiber types (p. 199)."[70]

Fiber Dimension and Lung Cancer Risk

For several decades, animal studies have supported the assertion that longer and thinner fibers (> 8 µm in length and ≤ 0.25 µm in width), including asbestos fibers, are more carcinogenic to lung and mesothelial tissues than shorter fibers. This has been called the "Stanton hypothesis."[94] In studies that involved pleural implants in rats, Stanton and colleagues found that longer and thinner fibers (i.e., > 8 µm in length and ≤ 0.25 µm in width) of a variety of different materials produced the highest correlation (correlation coefficient = 0.80) with probability of pleural tumors. However, shorter (5–8 µm) or wider (>0.25–1.5 µm) fibers were also reasonably correlated with tumor response (correlation coefficient = 0.63 and 0.68, respectively).[94–96] A series of studies by Davis et al in the 1970s and 1980s addressed fiber length and types and concluded that fibers > 10 µm in length were the more important ones in causing neoplastic responses in the lungs of rats.[97,98] Lippmann recently reviewed these and other studies and concluded that, since fibers between 0.3 and 0.8 µm in width have peak retention in the lung, and, given that the human alveolar macrophage is larger than the rat macrophage, asbestos fibers > 15 or 20 µm in length and > 0.15 µm in width are most closely associated with lung cancer.[99]

Very few epidemiological studies of asbestos and lung cancer have addressed the full range of fiber lengths, because they have principally relied on asbestos measurements that only counted fibers > 5 µm in length and > 0.25 µm in width (so-called regulated fibers), as required by regulations and dictated by feasibility. Indeed, there are only two epidemiological studies of asbestos-exposed workers with sufficient measurements to allow insight on the issue of fiber length. These studies addressed fiber dimensions in textile mills in South and North Carolina, based on retrospective measurements of archived dust samples using TEM. Stayner et al and Dement et al reported that more than 90% of the asbestos fibers in these archived samples were short and/or narrow (≤ 5 µm in length and/or <0.25 µm in width) and had not been counted by phase contrast microscopy in earlier studies.[100,101] They reevaluated the relationship between TEM-based fiber measurements and lung cancer risk and concluded that the strongest association was found between lung cancer and fibers > 10 µm and narrower than 0.25 µm.[100,102] However, they also found that very short and thin fibers (e.g., < 1.5 µm in length and < 0.25 µm in width) were associated with lung cancer risk. Fiber size categories were highly correlated in the dust samples from the South Carolina and North Carolina chrysotile textile factories, making it difficult to separate out the effect of fiber sizes.[100,102,103] Hamra et al applied a hierarchical model to the data from the North Carolina textile factory and found that the lung cancer risk associated with different fiber length–width groups was similar.[103]

Lung fiber burden studies add limited insights on this issue. Dodson and colleagues used TEM at 16,000 or 20,000 times magnification to examine the lung asbestos fiber burdens of 20 cases of lung cancer with known exposure to asbestos. They showed that 39 to 69% of detected asbestos fibers were ≤ 5 µm, and that the majority of both chrysotile and amphibole fibers would not have been counted by phase contrast microscopy (i.e., > 5 µm in length and ≥ 0.25 µm in width). Most counted fibers did not meet the dimensions

supported by the Stanton hypothesis (≥ 8 μm in length and < 25 μm in width) with chrysotile having the highest proportion of such fibers.[104] More recently, Adib and colleagues in Quebec used TEM to evaluate lung fiber burdens in cases of lung cancer, asbestosis, and mesothelioma among 123 workers from mining, maintenance, construction, and other industries.[105] Among lung cancer cases, chrysotile and tremolite, especially fibers < 5 μm, were the dominant fibers seen in the lungs. Among the subset of 13 lung cancer cases whose last exposure to asbestos was 30 or more years previously, chrysotile fibers were found in all cases, with short (<5 μm) fibers outnumbering longer (≥ 5 μm) by at least two- to threefold. Clearly, chrysotile fibers, especially short fibers, are capable of remaining in the lungs for long periods following exposure.

In summary, available data support the hypothesis that longer, thinner fibers have a stronger association with lung cancer than shorter, less thin fibers. However, there are empirical data in animals and epidemiological studies that support an association between shorter fibers and cancer.[94,102] Fiber burden studies show that short fibers, especially chrysotile, are very frequently present and often outnumber longer fibers in lung tissues of patients with a history of asbestos-related lung cancer, even many years after asbestos exposure ceased. Current evidence does not support the point of view that there is no cancer risk associated with exposure to short asbestos fibers.[66,96,106]

"Low Level" or Short Duration of Asbestos Exposure and Lung Cancer Risk

Studies completed in the past 10 years or so have confirmed and extended knowledge that lower levels of occupational exposure to all types of asbestos, including chrysotile, cause lung cancer. Loomis and colleagues[52] identified mortality patterns among workers at four North Carolina textile plants that used almost exclusively chrysotile asbestos and found an overall SMR of 1.96 (95% CI: 1.73–2.20); 277 workers had died from cancer of the lung or trachea. Among workers who worked for < 1 year and 1 to 5 years, the SMR was 1.82 (95% CI: 1.50–2.19) and 1.86 (95% CI: 1.45–2.34), respectively. Hein and others evaluated mortality among 3,072 workers at a South Carolina textile factory that used chrysotile asbestos and found an elevated SMR (1.54, 95% CI: 1.07–2.15) for workers with < 1.5 fiber/mL-year cumulative exposure; there was a clear trend of increasing lung cancer risk with increasing exposure.[53] Pira et al followed up 1,973 Italian textile workers exposed to mixed fiber types from 1946 to 1996 and found an overall SMR of 282 (95% CI: 222–354) for lung cancer. Lung cancer risk rose with duration of employment from SMR = 139 (based on 12 lung cancer deaths) among workers who worked < 1 year at the plant to a SMR = 250.8 among workers who worked 1 to <5 years at the plant, to a SMR = 530.9 among workers of > 10 years work at the plant.[107] Wang and colleagues evaluated nearly four decades of mortality among 1,012 chrysotile asbestos manufacturing workers in China and found that the group with "low level" exposure to asbestos had a hazard ratio of 1.94 (95% CI: 0.84–4.46) with a statistically significant trend of lung cancer risk with increasing exposure.[87] De Matteis et al studied 1,537 lung cancer cases from the general population in a Northern Italian case–control study and found a lung cancer OR of 1.76 (95% CI: 1.42–2.18) among those deemed to have low exposure to asbestos.[108] Gustavsson et al performed a population-based case–control study of 1,038 lung cancer cases in Stockholm, controlling for cigarette smoking, and found an OR of 1.90 (95% CI: 1.32–2.74) for cumulative exposure to asbestos of 4 fiber/mL-year of exposure to asbestos, and the risk on the lower end of the range of exposure was greater than that predicted by a linear dose–response relationship.[109] In an earlier study, Seidman et al studied amosite asbestos manufacturing workers in New Jersey and found a 3-fold increase in lung cancer deaths among workers who worked less than 1 year in the plant, which rose to 5.6-fold for workers who worked between 1 and 2 years, and 6.5-fold for workers who worked over 2 years.[110]

Threshold and Risk of Lung Cancer and Mesothelioma

The current consensus is that there is no known safe level of exposure to asbestos.[3,18,70,72] Stated otherwise, no threshold has been demonstrated below which there is no identified risk of cancer related to asbestos. This view is based on several lines of evidence, specific and nonspecific to asbestos. Current risk assessment guidelines in the United States support linear extrapolation from the known dose–response curve to lower levels of exposure for DNA-reactive agents.[111] Although the exact mechanisms of asbestos carcinogenesis are not known at present, asbestos fibers, including chrysotile, are genotoxic and are, therefore, "DNA reactive."[16,112,113]

Studies of asbestos-exposed cohorts provide evidence that a threshold for cancer risk has not been established for asbestos. Stayner et al evaluated alternative exposure–response models using data from a South Carolina textile factory.[114] The study of asbestos-related diseases at this South Carolina textile factory was judged to employ one of the highest quality exposure assessments available in the published literature on asbestos-related disease.[60] They found that the best model for lung cancer was linear on a multiplicative scale with the best data fit obtained when the threshold was set at zero. Referring to asbestos exposure, the authors concluded that "there was absolutely no significant evidence for a threshold in …lung cancer." In a recent meta-analysis, van der Bij et al used a variety of statistical models to examine the issue of lung cancer risk associated with relatively low exposure to asbestos and found that a natural spline model best fit the data.[72] They note that no threshold for lung cancer risk due to asbestos exposure has been identified.[72] In a recent systematic review of asbestos and lung cancer, Nielsen and colleagues report that most relevant meta-analyses have been predicated on linear dose–response relationship models, suggesting no exposure threshold for lung cancer risk.[57,60,70,72] Nielsen et al concluded that there "is no evidence for a no observed effect level concerning asbestos-related lung cancer."

Studies detailing the occurrence of malignant mesothelioma and lung cancer at low levels of asbestos exposure were described in previous sections.

Some have hypothesized that asbestos-related lung cancer occurs only in people with asbestosis, and, since the latter appears to have a threshold, a threshold also exists for asbestos-related lung cancer. However, epidemiological studies show that asbestos-related lung cancer occurs in the absence of asbestosis (see above section), undermining this hypothesis.

Mechanisms of Asbestos-Related Lung Cancer

Multiple mechanisms are likely to be involved in asbestos-related carcinogenesis. Excellent recent reviews are available.[112,115,116] Asbestos causes a wide variety of cellular responses, and it is likely that several these responses relate to pathways that lead to cell transformation and cancer. Asbestos is mutagenic and genotoxic.[113,115] Asbestos fibers provoke the formation of reactive oxygen species that lead to oxidation of DNA bases and DNA strand breaks[16,112]; this is considered an indirect form of genotoxicity. In addition to causing oxidative stress, asbestos also alters several antioxidant pathways that restrain the cells' ability to limit damage caused by the reactive free radicals that produce oxidative stress.[112] Some of these cellular responses are also likely to underlie fibrogenesis. Asbestos may additionally interfere with DNA repair processes.

Asbestos directly interferes with mitosis during cell division, causing genetic damage in daughter cells.[116] A variety of chromosomal abnormalities caused by asbestos fibers have been described.[112] An additional carcinogenic mechanism of asbestos is the absorption of other carcinogens on the fiber surface (e.g., polycyclic aromatic hydrocarbons), which may also help explain the joint interactive effect of asbestos and other exposures (e.g., smoking). Cell death (apoptosis), a mechanism to limit proliferation of transformed cells, is also altered by asbestos.

Screening for Asbestos-Related Lung Cancer

Japanese and American investigators demonstrated in the late 1990s that low-dose CT scanning could detect early-stage lung cancers in high-risk smokers.[117,118] Henschke et al subsequently reported a 92% projected 10-year survival among 302 individuals with screen-detected Stage 1 lung cancer who underwent surgery.[119] In 2011, the National Lung Screening Trial, a randomized controlled trial of more than 53,000 people conducted by the U.S. National Cancer Institute, was halted when data review indicated that the CT-screened arm had experienced a significant 20% lung cancer mortality reduction and a 6.7% overall mortality reduction compared with reference group who had received a chest radiograph.[120] Occupational risk of lung cancer was not a risk factor included in the studies.[120]

In 2013, United States Preventive Services Task Force endorsed the use of this test for people who are at high risk of lung cancer, though they used only smoking and age to define high risk.[121] More recently, the National Comprehensive Cancer Network, a collaboration of many of the most prestigious cancer centers in the United States, recommended low-dose CT for people 50 years and older who had a 20- or more pack-year history of cigarette smoking and one additional risk for lung cancer, including occupational exposure to asbestos or selected other occupational lung carcinogens.[122] The American Association of Thoracic Surgery has similar guidelines.[123]

Use of low-dose CT scanning for early lung cancer detection offers an unprecedented opportunity to detect lung cancer at an early stage in asbestos-exposed workers and to prevent much of the excess lung cancer mortality that has been so well documented during the past 70 years. Occupational medicine physicians, pulmonary physicians, and other occupational health professionals have an essential role in educating, organizing, and promoting lung cancer screening for asbestos-exposed workers.

Disclosure

Dr. Markowitz has provided expert witnesses services in tort lawsuits involving issues of asbestos-related diseases.

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